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# High Throughput In-Silico Screening Against Flexible Protein Receptors

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Results for the screening of known ligand databases versus rigid and flexible receptors are presented using an all-atom model and a very efficient optimization method. The results are compared with other programs and a better performance is shown.

## 1 Introduction

Virtual screening of chemical databases to targets of known threedimensional structure is developing into an increasingly reliable method for finding new lead candidates in drug development. Based on the stochastic tunneling method (STUN[1]) we have developed FlexScreen[2,3], a novel strategy for high-throughput in-silico screening of large ligand databases. Each ligand of the database is docked against the receptor using an all-atom representation of both ligand and receptor. In the docking process both ligand and receptor can change their conformation. The ligands with the best evaluated affinity are selected as lead candidates for drug development. Using the thymidine kinase inhibitors as a prototypical example we documented the shortcomings of rigid receptor screens in a realistic system. We demonstrate a gain in both overall binding energy and overall rank of the known substrates when two screens with a rigid and flexible (up to 15 sidechain dihedral angles) receptor are compared. We note that the STUN suffers only a comparatively small loss of efficiency when an increasing number of receptor degrees of freedom is considered. FlexScreen thus offers a viable compromise between docking flexibility and computational efficiency to perform fully automated database screens on hundreds of thousands of ligands.

## 2 Methodology

*Docking Method:* Stochastic optimization with STUN: Non-linear transformation of the potential energy surface using

$$E_{\mathrm{STUN}}(x) = \ln\left(x + \sqrt{x^2+1}\right) \ , \tag{1}$$

with $x = \gamma\,(E - E_0)$, $\gamma = 0.05$ Mol/kJ and $E_0$ is the lowest energy encountered during the simulation.

*Scoring Function:*

$$S = \sum_{Protein} \sum_{Lig.,fl.SC.} \left(\frac{R_{ij}}{r_{ij}^{12}} - \frac{A_{ij}}{r_{ij}^{6}} + \frac{q_i q_j}{r_{ij}}\right) + \sum_{h-bonds} \cos\,\Theta_{ij} \left(\frac{\tilde{R}_{ij}}{r_{ij}^{12}} - \frac{\tilde{A}_{ij}}{r_{ij}^{10}}\right) \tag{2}$$

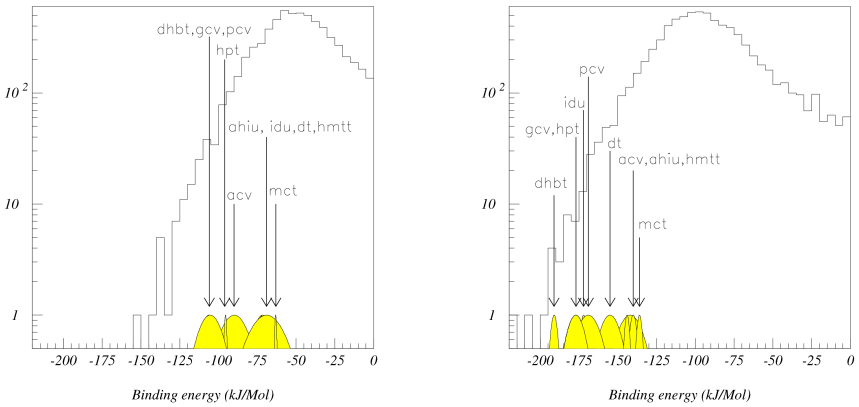


Figure 1. Binding energies of the docked substrates. Left side, rigid screening with total score 4206. Right side, flexible screening with total score 8083.

Partial charges $q_i$ are usually evaluated with InsightII and ESFF forcefield, Lennard-Jones parameters $R_{ij}$, $A_{ij}$ from OPLSAA or from AutoDock and Hydrogen bond parameters $\tilde{R}_{ij}$, $\tilde{A}_{ij}$ from AutoDock.

## 3 Results

*Screen with rigid (1e2n) receptor:* A receptor has many possibilities to adapt to different inhibitors. Choosing one fixed receptor for all type of ligands restricts the amount of possible binding modes to only a few and therefore some ligands loose their specificity to this receptor. In 1e2n the receptor cavity is rather wide and many different ligands can fit into the cavity; but distinctive binding modes are missing for many ligands. Therefore the 10 known substrates of TK are energetically close to each other (see fig 1, left side), but because of the lack of specific binding modes they score worse than many ligands of the database.

*Screen with flexible (1e2n) receptor:* To model the receptor flexibility, we made 6 bonds of 4 side-chains flexible to allow the substrates to find their characteristic binding motif. Compared with the database all 10 ligands get lower affinities now (see fig 1, right side).

*Astex data set results:* The results from table 1 show that *FlexScreen* is either of similar accuracy (Glide) or significantly more accurate (Gold, FlexX). Additionally *FlexScreen* proved to reliably find the correct binding modes. In **89%** of the cases FlexScreen yielded a binding mode with a RMS deviation of less than 2.0 Å and performed therefore better than Gold, Glide and FlexX.

| | FlexScreen | Glide | Gold | FlexX: |
|---|---|---|---|---|
| FlexScreen wins/total | | 33/59 | 20/27 | 40/59 |
| Results $< 2.0$Å | 77/86 | 41/59 | 20/27 | 32/59 |

Table 1. Summary of the docking results; compared are the RMS values of the different docking codes for the Astex data set and the percentage of cases having a RMS <2.0 Å.

## 4 Conclusion

Using side-chain flexibility (15 selected rotational bonds), all substrates ranked within the upper 10% of the database. The binding energy is substantially lowered for all of the ligands which supports the assumption that the receptor is now sufficiently able to adopt to the docking ligand and to model their specific binding motif, which can be compared with the x-ray receptor-ligand complex. Concerning the accuracy and reliability of finding the experimental binding mode *FlexScreen* proved to be of better performance than the three other docking programs (Glide, Gold and FlexX).

## 5 Acknowledgments

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